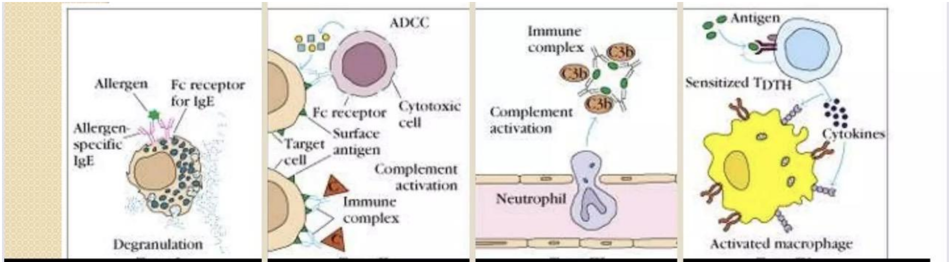
ANAPHYLAXIS

Anaphylaxis is a severe, systemic allergic reaction with multisystem involvement, including the skin, airway, vascular system, and GI.

- **Anaphylactic shock** is a severe, potentially life-threatening allergic reaction leading to sudden cardiovascular collapse. It can occur within seconds or minutes of exposure to allergen.

Types of hypersensitivity (Allergic Reaction)

- Type I: Immediate Hypersensitivity
- Type II: Cytotoxic Hypersensitivity
- Type III: Immune Complex Hypersensitivity
- Type IV: Delayed Hypersensitivity


Allergen
Fc receptor for IgE
Allergen-specific IgE
Degranulation
ADCC
Fc receptor
Cytotoxic cell
Target cell
Surface antigen
Complement activation
Immune complex
Immune complex
C3b
C3b
C3b
Complement activation
Neutrophil
Antigen
Sensitized TDTH
Cytokines
Activated macrophage

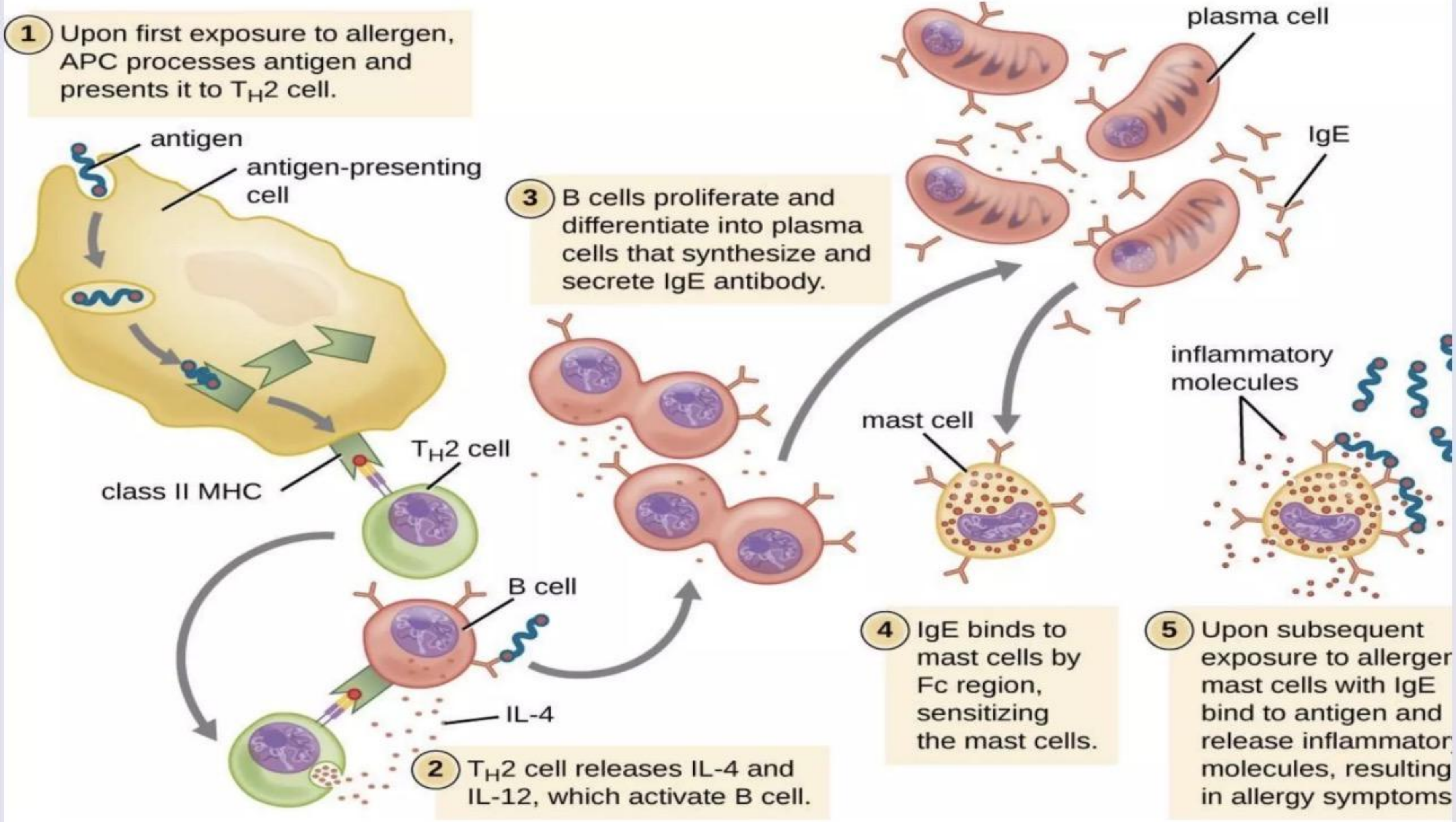
Type I	Type II	Type III	Type IV
IgE Mediated	IgG/IgM Mediated	IgG Mediated	T cell
Classic Allergy	rbc lysis	Immune complex Disease	Delayed Type Hypersensitivity

Anaphylactic reaction	***Anaphylactoid reaction***
It is an immune- mediated reaction.	***It is a non- immune mediated reaction.***
IgE antibody plays an important role .	***No relation with IgE antibody.***
The allergen[antigen] reacts with the IgE antibody and the complex causes degranulation of the mast cells and hence release of histamine and other mediators.	***The allergen[antigen] causes direct release of histamine and other mediators from the mast cell and does not cause degranulation.***

PATHOPHYSIOLOGY:-

World Allergy Organisation classifies Anaphylaxis:-

- ❖ **Immunologic anaphylaxis** — Immunologic anaphylaxis includes:
  - IgE-mediated reactions
  - Immune complex/complement-mediated reactions
- ❖ **Non-immunologic anaphylaxis** - caused by agents or events that sudden, massive mast cell or basophil degranulation, without the involvement of antibodies.


antigen
antigen-presenting cell
class II MHC
T_H2 cell
B cell
IL-4
plasma cell
IgE
mast cell
inflammatory molecules

1. Upon first exposure to allergen, APC processes antigen and presents it to T_H2 cell.

2. T_H2 cell releases IL-4 and IL-12, which activate B cell.

3. B cells proliferate and differentiate into plasma cells that synthesize and secrete IgE antibody.

4. IgE binds to mast cells by Fc region, sensitizing the mast cells.

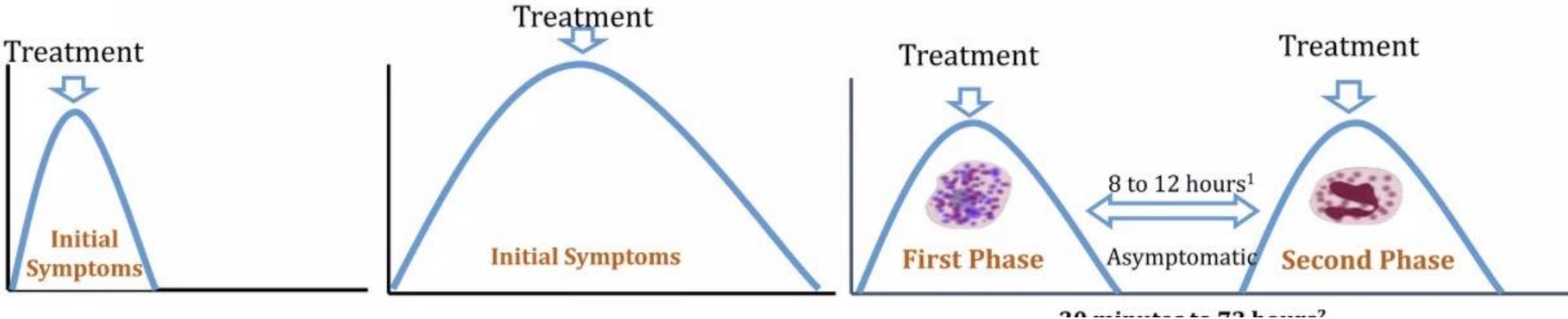
5. Upon subsequent exposure to allerge mast cells with IgE bind to antigen and release inflammator molecules, resulting in allergy symptoms

Chemical mediators of anaphylaxis

Mediators	***Physiological effects***
Histamine	✓***Increased capillary permeability*** ✓***Peripheral vasodilation*** ✓***Bronchoconstriction*** ✓***Utricaria***
Leukotrienes	✓***Increased capillary permeability*** ✓***Bronchoconstriction*** ✓***Negative ionotropy*** ✓***Coronary artery vasoconstriction***
Prostaglandins	✓***Bronchoconstriction***
Eosinophil chemotactic factor	✓***Attraction of eosinophils***
Platelet - activating factor	✓***Platelet aggregation*** ✓***Release of vasoactive amines***

Types of Reaction

- **Uni-Phasic** – The most common type, 80-90% of all cases. Isolated reaction producing signs and symptoms within minutes (typically within 30 minutes) of exposure to an offending stimulus
- **Protracted** – Severe anaphylactic reaction that may last between 24 and 36 hours despite aggressive treatment
- **Bi-Phasic** – Late-phase reactions that can occur 1 to 72 hours (most within 10 hours) after the initial attack (1%-23%)


Treatment
Initial Symptoms
Treatment
Initial Symptoms
Treatment
Treatment
8 to 12 hours¹
First Phase
Asymptomatic
Second Phase
30 minutes to 72 hours²

Pathophysiology

Two Phases

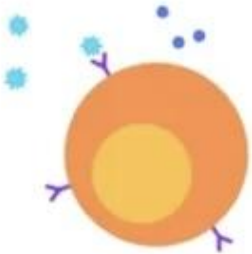
- Immediate (minutes)
- Late (Hours)

Antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine) and tryptase (a marker of mast cell activation)

Chemokines attract inflammatory cells, eg, eosinophils) and cytokines (eg, leukotrienes) from mast cells → inflammation and tissue damage

5 Stages of Allergic Reaction

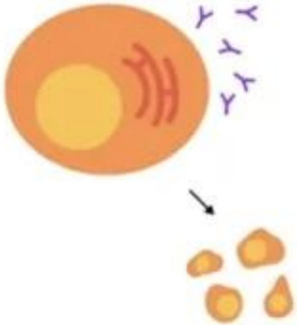
1



Sensitization

Initial Exposure.
Body Produces IGE
antibodies

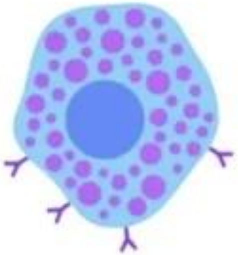
2



Early Phase

Re-exposure.
Mast Cells release
histatime

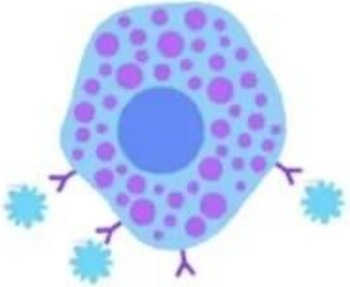
3



Cellular Recrritment

Inflamatory cells
(hours later)

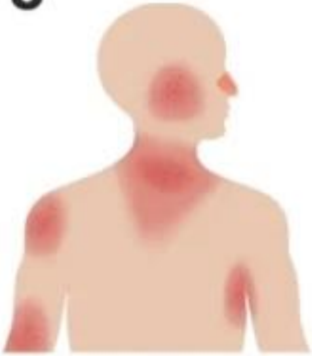
4



Late Phase

Sustained Inflamation
(hours later)

5



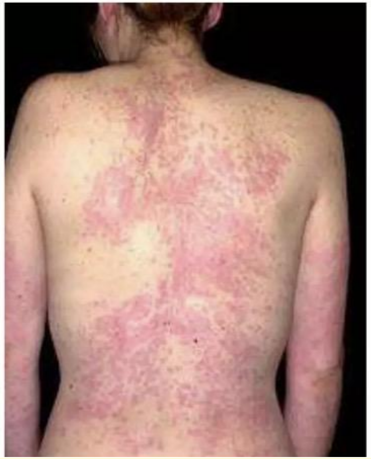
Anaphylaxis

Blood pressure drops
suddenly and the
airways narrow,
blocking breathing.

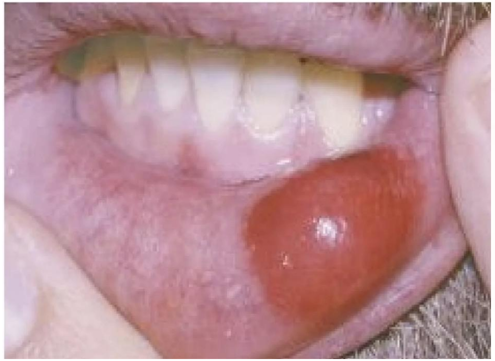
Signs and Symptoms

Skin	Feeling of warmth, flushing (erythema), itching, urticaria, angioedema, and pilor erection
Respiratory	Nose – Itching, congestion, rhinorrhea, and sneezing. Laryngeal – Itching and tightness in the throat, dysphonia, hoarseness, stridor Lower airways – Dyspnea, chest tightness, cough, wheezing, and cyanosis.
Gastrointestinal	Nausea, abdominal pain, vomiting, diarrhea, and dysphagia.
Cardiovascular	Felling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia, or other dysrrhythmia, hypotension, tunnel vision, hearing,..
Neurological	Anxiety, apprehension, sense of impending doom, seizures, headache and confusion...

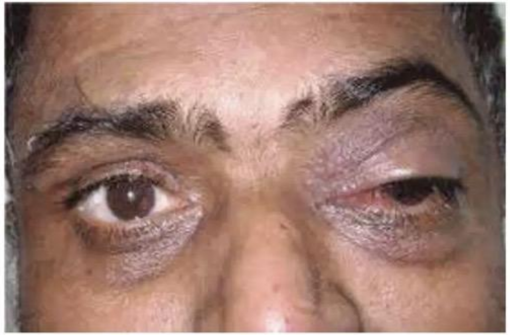
hives

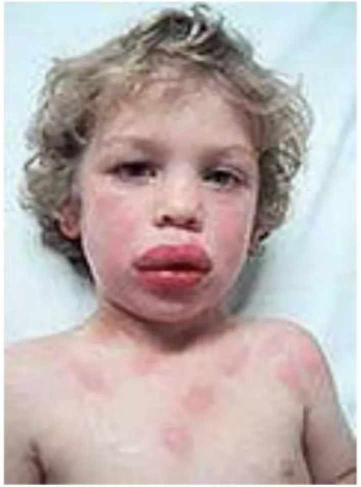


Anaphylactoid purpura

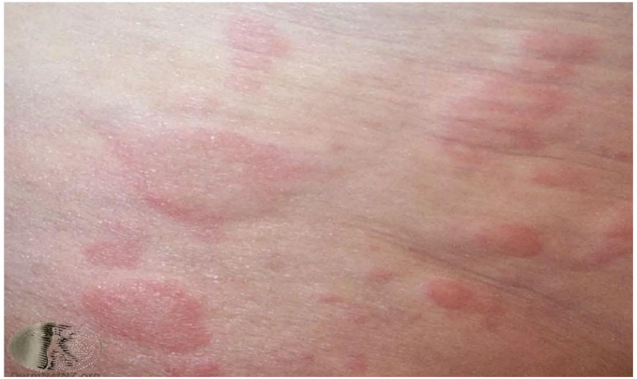


Swelling of conjunctiva

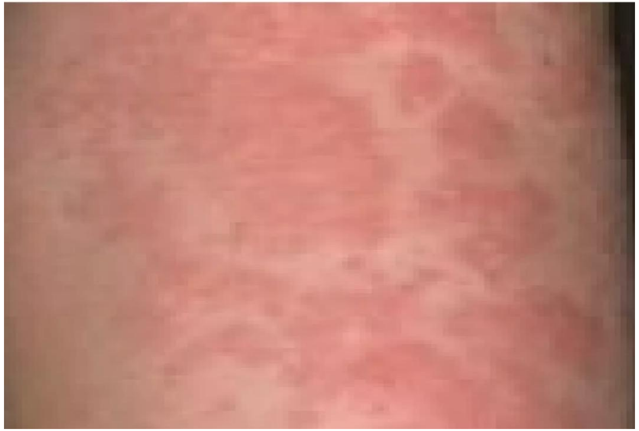




Urticaria



Erythematous Patches



Risk factors:

- Asthma -increased risk of anaphylaxis if asthma is uncontrolled
- Elevated baseline tryptase level indicates possible mast cell disorder
- Previous sensitization and formation of antigen-specific IgE with history of anaphylaxis.
- Concomitant use drugs: beta-adrenergic blockers, ACE inhibitors, NSAIDs, alcohol, etc.
- Cofactors such as exercise, fever, acute infection and emotional.

Diagnostic Criteria

Acute onset of an illness with involvement of the skin, mucosal tissue, or both

AND AT LEAST 1 OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm)
- Reduced BP or associated symptoms of end-organ dysfunction

OR

≥2 of the following that occur rapidly after exposure to a likely allergen (minutes to several hours)

- Involvement of the skin mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
- Reduce BP* or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

OR

Reduced BP after exposure to known allergen (minutes to several hours)

- Infants and children - Low SBP (age-specific)* or greater than 30% decrease in SBP
- Adults – SBP of less than 90mmHg or greater than 30% decrease from that person's baseline

INTRA -OPERATIVE ANAPHYLACTIC REACTIONS

- The risk of perioperative anaphylaxis is reported as between 1:3,500 and 1:20,000 with the mortality rate of 4% and an additional 2% surviving with severe brain damage.
- More than 90% of the allergic reactions evoked by Intravenous drugs occur within the 5 minutes of administration.

ROLE OF AN ANAESTHESIOLOGIST

- Thorough preoperative evaluation of→FOOD, SPECIFIC DRUG ALLERGIES.
- Detailed description regarding previous anaphylactic reaction and the treatment given for it should be mentioned in the PAC CHART.
- Ask specifically about episode of anaphylaxis due to general anaesthetic drugs or during regional anaesthesia.

- If the patient is found to be allergic to specific drugs, it should be conveyed to the surgeon as well as the OT staff regarding the allergic reaction
- Mention in the PAC and intraoperative chart in→CAPITAL LETTERS regarding it.
- Preoperative testing for allergies should be conducted.

Agents causing Allergic reactions

- **Non-pharmacological agents**- pollen grains, dust, animal dander, mushrooms, bee-stings, sea-food, scorpion bites, poisonous plants etc.
- **Pharmacological agents-**
- Antibiotics- penicillins, cephalosporins, fluoroquinolones, vancomycin, sulfonamides, B-lactams →incidence of cross sensitivity among allergic reactions between penicillins and cephalosporins. Hence, perioperative ANTIBIOTIC SENSITIVITY TESTING using a test dose of the antibiotic to be used during surgery.

- NSAIDS- aspirin, diclofenac, ibuprofen, paracetamol →cross-sensitivity
- IV contrast agents →methylene blue dyes, gadolinium contrast etc.
- Drugs like Insulin, Protamine, Aprotinin
- Bone cement - PMMA ie; polymethyl- methacrylate.
- IV fluids ie: colloids like hexaethyl starch, dextran, albumin
- Blood products

Anaesthetic drugs causing anaphylaxis

- **Muscle relaxants**- approximately 50-60% of anaesthetic allergic reactions.

❖ Benzylisoquinolinium compounds (more likely)- atracurium, mivacurium.

❖ Aminosteroid compounds (less likely)-pancuronium, vecuronium, rocuronium.

❖ Succinylcholine contains a flexible molecule that can cross-link between mast cell igE receptors and, thus, induce mast cell degranulation

INDUCTION DRUGS

they account for 5% of anaphylactic events that occur perioperatively.

1. Thiopentone- more commonly due to release of histamine.
2. Propofol- more commonly due to its contents like egg lecithin, soybean emulsion. Hence, in patients having allergy to egg and soya, propofol should be avoided.
3. Allergic reactions to etomidate, ketamine and midazolam are very rare.

LOCAL ANAESTHETICS

They account for less than 2 % of allergic reactions.

1. Ester-type: [more likely]: cocaine, tetracaine, benzocaine etc.

2. Amide type:[less likely]: Lignocaine, bupivacaine, ropivacaine.

Esters cause more allergic reactions than amides because they get metabolised to para-aminobenzoic acid which is a highly antigenic compound.

Opioids

less than 3% of anaphylactic reactions.

1. Morphine, codeine: they directly cause release of histamine from mast cells and basophils.

2. Fentanyl: less likely to cause an allergy.

LATEX

- Natural Rubber Latex is the milky, white fluid derived from the Hevea brasiliensis tree and is a component of most sterile and nonsterile gloves used in the perioperative period.
- NRL →operating room products, including tourniquets, face masks, Ambu bags, and Foley catheters.
- The high demand for latex gloves led to a decrease in manufacturing time, which in turn led to an **increased protein content in gloves.**
- This led to increase in the incidence of latex anaphylaxis

- Common fruits or foods that cross-react with latex include mango, kiwi, chestnut, avocado and banana.
- Latex exposure is more likely with parenteral or mucous membrane exposure but can also occur with cutaneous contact or via latex aeroallergens.
- Latex-specific IgE can be detected in the patient's serum by RAST and the enzyme-allergosorbent test.
- Avoidance is the only effective treatment at the present time and consists of latex-free gloves and operating room equipment.

DIAGNOSIS

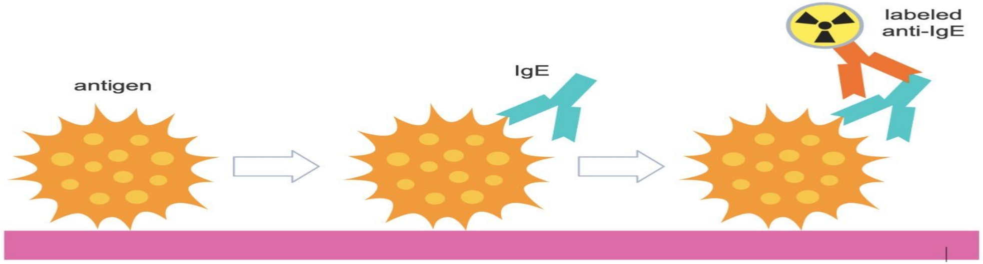
- The initial diagnosis of perioperative anaphylaxis relies on the **history** and **hemodynamic changes** and **clinical findings** intraoperatively.
- **Serum tryptase** (normal range 1-15 ng/ml)is a mast cell protease that is increased in cases of anaphylaxis, signaling an immune-mediated mechanism.
- An increase in ser. Tryptase level →1st sample to be taken immediately after first sign of anaphylaxis →2nd sample to be taken after 1-2 hours and correlate with baseline level.
- Tryptase half-life is **2 h**, and the levels gradually decrease over time.

DIAGNOSIS

- Histamine in serum is not measured routinely because of its half-life of only a few minutes
- Collections of urine histamine for 24 h after the anaphylactic episode will reflect the release from mast cells and basophils.

• Radioallergosorbent test (RAST)

- This test measures the presence of specific gE antibodies in serum that bind to a disk coupled with the specific drug and can be performed if the patient has extensive skin lesions, is receiving drugs such as antihistamines, or has presented with a recent episode of anaphylaxis.
- RAST tests are highly specific, but the sensitivity is low for most drugs.



- Skin allergy testing (such as patch testing) is available for certain foods and venoms. Blood testing for specific IgE can be useful to confirm milk, egg, peanut, tree nut and fish allergies.

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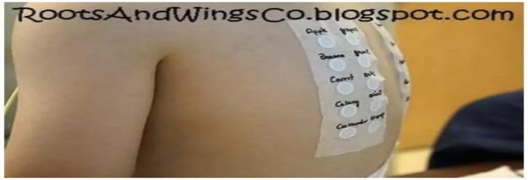
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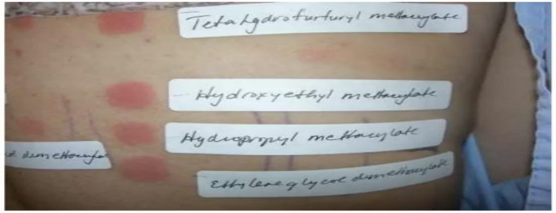

Tetrahydrofurfuryl methacrylate
Hydroxyethyl methacrylate
Hydroxypropyl methacrylate
dimethacrylate
Ethylene glycol dimethacrylate

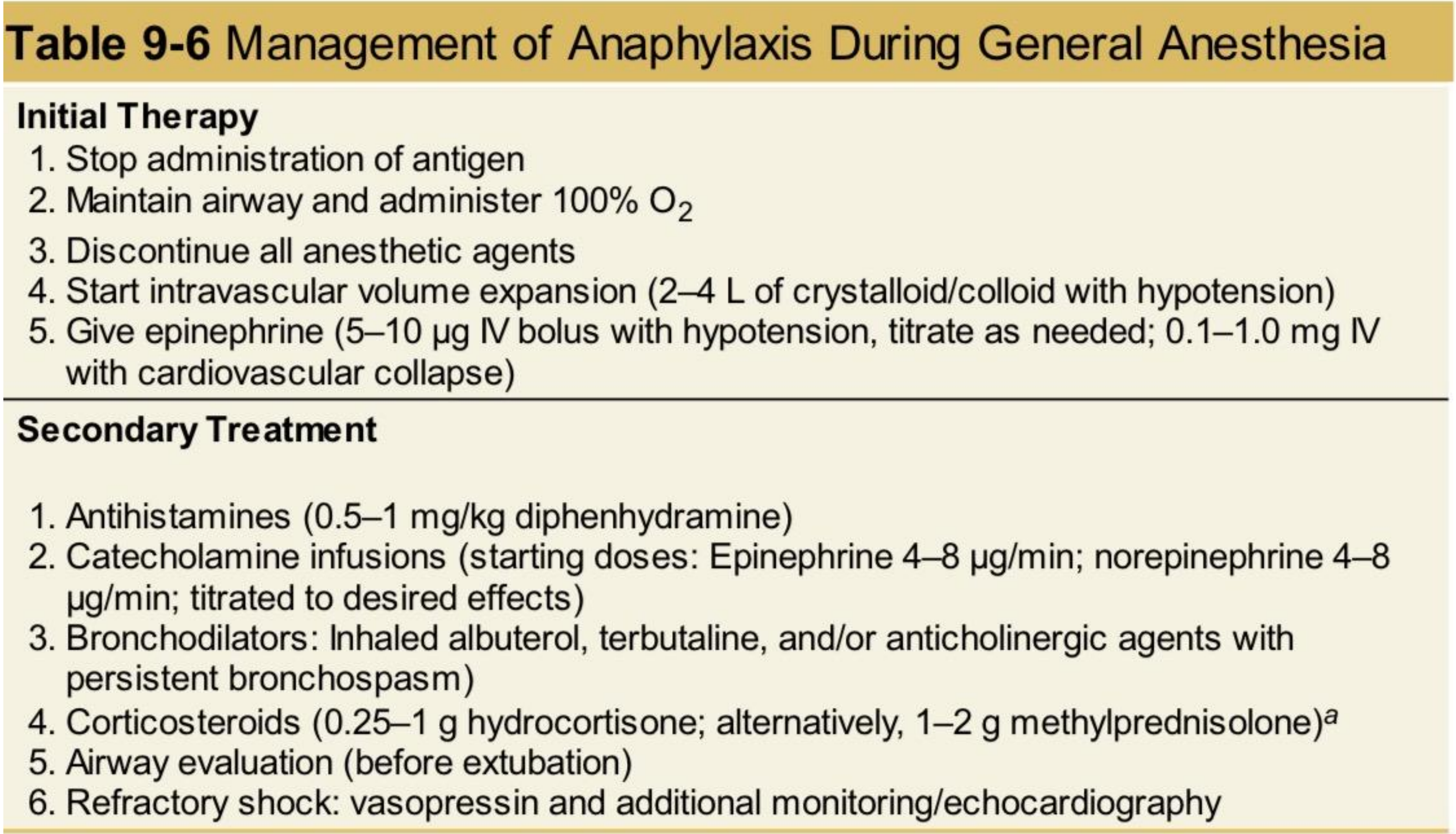


Table 9-6 Management of Anaphylaxis During General Anesthesia

Initial Therapy

1. Stop administration of antigen
2. Maintain airway and administer 100% O_2
3. Discontinue all anesthetic agents
4. Start intravascular volume expansion (2–4 L of crystalloid/colloid with hypotension)
5. Give epinephrine (5–10 µg IV bolus with hypotension, titrate as needed; 0.1–1.0 mg IV with cardiovascular collapse)

Secondary Treatment

1. Antihistamines (0.5–1 mg/kg diphenhydramine)
2. Catecholamine infusions (starting doses: Epinephrine 4–8 µg/min; norepinephrine 4–8 µg/min; titrated to desired effects)
3. Bronchodilators: Inhaled albuterol, terbutaline, and/or anticholinergic agents with persistent bronchospasm)
4. Corticosteroids (0.25–1 g hydrocortisone; alternatively, 1–2 g methylprednisolone)[a]
5. Airway evaluation (before extubation)
6. Refractory shock: vasopressin and additional monitoring/echocardiography

Epinephrine administration:

Titrate the dose according to symptom, severity and clinical response.

- Epinephrine used S/C in the dose of 0.3mg-0.5 mg if the patient is **not** in a state of shock.

In case of shock, S/C injection is not helpful due to decreased tissue perfusion. Hence, IV INJECTION IS GIVEN. Adults- 10 mcg to 1 mg by bolus IV, repeat every 1-2 min as needed.

- IV infusion starting at 0.05-1 mcg/kg/min

Children- 1-10 mcg/kg by bolus, repeat every 1-2 min as needed.

- **EPINEPHRINE is life - saving drug in anaphylactic reactions and shock.**

Effects of EPINEPHRINE

- Increases BP, reverses peripheral vasodilation (alpha-adrenergic activity)
- Reduces urticaria and angioedema by vasoconstriction (alpha-adrenergic activity)
- Bronchodilation - relaxes bronchial smooth muscle (beta-2 adrenergic activity)
- Increases cardiac contractility - force and volume, increasing heart rate & BP (beta-1 adrenergic activity)
- Prevents further mast cell degranulation (beta-1 adrenergic activity)

Epinephrine Auto-injectors

EpiPen Jr.
EpiPen

- **Epipen**
  - Epipen Jr. (0.15 mg)
  - Epipen (0.30 mg)
  - One dose: auto-injection

Twinject
Twinject

- **Twinject**
  - Twinject 0.15
  - Twinject 0.30
  - Two doses: first is an auto-injection, second dose is manual

INOTROPES

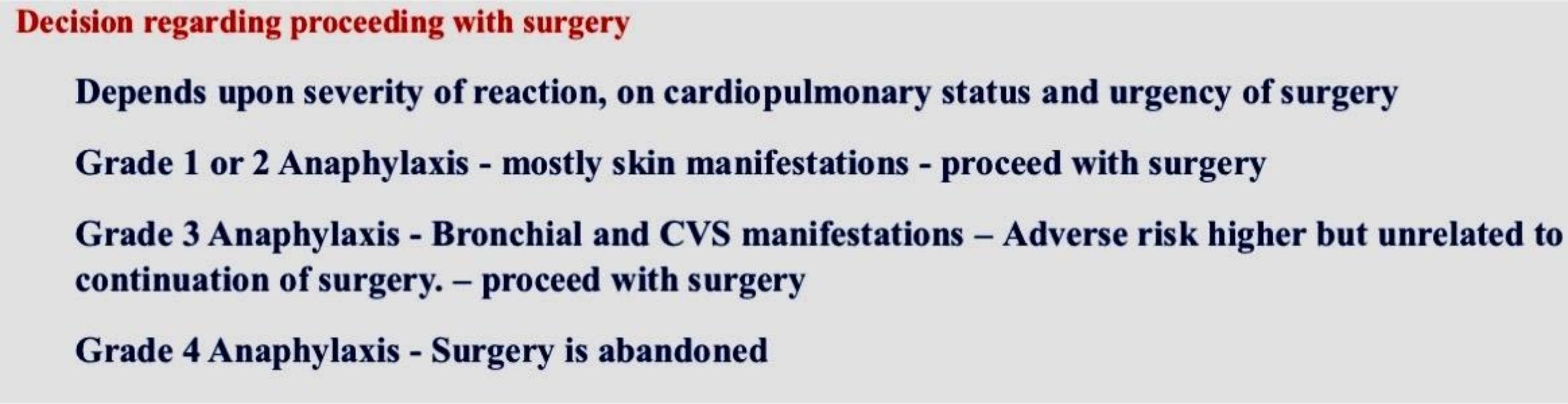
- **Vasopressin** for refractory hypotension (1 to 2 units bolus or infusion).
- **Norepinephrine** infusion for refractory hypotension as an alternative (2 to 10 mcg/minute titrated to effect).
- Consider **glucagon** (1 to 5 mg slow IV bolus over 5 minutes) for refractory shock if patient has received high-dose beta-blockers.

ANTIHISTAMINES-**Diphenhydramine HCL/Avil**

- For 25 to 50 mg can be administered IV over five minutes, which may be repeated up to a maximum daily dose of 400 mg per 24 hours.
- For children weighing less than 50kg, diphenhydramine 1 mg/kg (maximum 50 mg) can be administered IV over five minutes, which may be repeated up to a maximum daily dose of 5 mg/kg or 200 mg per 24 hours.
- **H2 antihistamines**: Famotidine: 20 mg IV (or cimetidine).

Grade	Summary	Specific signs and symptoms
Grade 1	Generalised mucocutaneous signs	Erythema Urticaria Angioedema
Grade 2	Multi-organ manifestations	Mucocutaneous signs Bronchospasm Hypotension
Grade 3	Severe life threatening multi-organ manifestations	Arrhythmia Cardiovascular collapse Bronchospasm Can have cutaneous signs
Grade 4	Cardiopulmonary arrest	Cardiac arrest

Figure 1: Grading of anaphylaxis, adapted from the Ring and Messmer grading scale[7]



Decision regarding proceeding with surgery

Depends upon severity of reaction, on cardiopulmonary status and urgency of surgery

Grade 1 or 2 Anaphylaxis - mostly skin manifestations - proceed with surgery

Grade 3 Anaphylaxis - Bronchial and CVS manifestations – Adverse risk higher but unrelated to continuation of surgery. – proceed with surgery

Grade 4 Anaphylaxis - Surgery is abandoned